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(54) Title: NEW SUBSTITUTED 1-PHENYL-TETRAHYDRONAPHTALENE DERIVATIVES AND THEIR USE AS INHIBITORS OF IGF-1 RECEPTOR

(57) Abstract: The invention refers to new compounds belonging to the group of substituted 1-phenyl-tetrahydronaphtalenes and the use thereof as inhibitors of the insulin-like growth factor-1 receptor. Said compounds can be used for treatment of IGF-1R dependent diseases, such as cancer, psoriasis, arteriosclerosis and acromegaly.

NEW SUBSTITUTED I-PHENYL-TETRAHYDRONAPHTALENE DERIVATIVES AND THEIR USE AS INHIBITORS OF IGF-1 RECEPTOR.

The present invention refers to new compounds as well as to the use of said new compounds as specific inhibitors of the insulin-like growth factor-1 receptor, the IGF-1R, for treatment of IGF-1R dependent diseases, such as cancer, psoriasis, and arteriosclerosis.

BACKGROUND OF THE INVENTION

The insulin-like growth factor-1 receptor plays an important role in proliferation, protection against apoptosis and transformation of malignant cells. The IGF-1R is also important for maintaining the malignant phenotype of tumour cells, and is involved in tumour cells developing resistance to the action of anti-cancer drugs. In contrast, the IGF-1R seems not to be an absolute requirement for normal cell growth.

The IGF-1R consists of two identical extracellular alpha-subunits that are responsible for ligand binding, and two identical beta-subunits with a transmembrane domain and an intracellular tyrosine kinase domain. The ligand-receptor interaction results in phosphorylation of tyrosine residues in the tyrosine kinase domain, which spans from amino acid 973 to 1229 of the β-subunit. The major sites for phosphorylation are the clustered tyrosines at position 1131, 1135 and 1136 (LeRoith, D., et al., Endocr Rev 1995 April; 16(2), 143-63). After autophosphorylation, the receptor kinase phosphorylates intracellular proteins, like insulin receptor substrate-1 and Shc, which activate the phosphatidyl inositol-3 kinase and the mitogen-activated protein kinase signalling pathways, respectively.

Based on the pivotal role of IGF-1R in malignant cells, it becomes more and more evident that IGF-1R is a target for cancer therapy (Baserga, R., et al., Endocrine vol. 7, no. 1, 99-102,

August 1997). One strategy to block IGF-1R activity is to induce selective inhibition of the IGF-1R tyrosine kinase.

Drugs containing the notoriously toxic cyclolignan podophyllotoxin have been used for centuries, and its anti-cancer properties have attracted particular interest. Undesired and severe side effects of podophyllotoxin have, however, prevented its use as an anti-cancer drug. The mechanism for the cytotoxicity of podophyllotoxin has been attributed to its binding to beta-tubulin, leading to inhibition of microtubule assembly and mitotic arrest. A cyclolignan with a lactone ring in a trans configuration as in podophyllotoxin has been shown to be required for binding to beta-tubulin.

During the last decades the major interest in podophyllotoxin derivatives has concerned etoposide, which is a ethylidene glucoside derivative of 4´-demethyl-epipodophyllotoxin. Etoposide, which has no effect on microtubules (or the IGF-1R), is a DNA topoisomerase II inhibitor, and is currently being used as such in cancer therapy.

PRIOR ART

The IGF-1R is a member of the tyrosine kinase receptor family, which also includes the receptors of insulin, epidermal growth factor (EGF), nerve growth factor (NGF), and platelet-derived growth factor (PDGF). A number of synthetic tyrosine kinase inhibitors, called tyrphostins, have been studied by Párrizas, M., et al., Endocrinology 1997, Vol. 138, No. 4, 1427-1433. The major disadvantage with all tyrphostins active on IGF-1R is that they cross-react with the insulin receptor, since these receptors are highly homologous. However, some of the tyrphostins showed a moderate preference for IGF-1R, suggesting that it could be possible to design and synthesize small molecules capable of discriminating between these two receptors.

Substrate competitive inhibitors of the IGF-1 receptor kinase are discussed by Blum, G., et al. in Biochemistry 2000, 39, 15705-15712. A number of lead compounds for inhibitors of the isolated IGF-1R kinase are reported. The search for these compounds was aided by the knowledge of the three-dimensional structure of the insulin receptor kinase domain, which is 84 % homologous to the IGF-1R kinase domain. The most potent inhibitor found was tyrphostin AG 538, with an IC_{50} value of 400 nM. However, said inhibitor also blocked the insulin receptor kinase.

PCT/SE02/01223 discloses new compounds, i.e. substituted 1-phenyl-tetrahydronaphtalenes, and the use thereof as well as the use of cyclolignans having a trans configuration in the lactone ring as specific inhibitors of the insulin-like growth factor-1 receptor. Said compounds can be used for treatment of IGF-1R dependent diseases, especially cancer. Before this, a connection between the IGF-1R and podophyllotoxin derivatives/cyclolignans had never been made.

The Chemistry of Podophyllum by J.L. Hartwell et al., Fortschritte der Chemie organischer Naturstoffe 15, 1958, 83-166, gives an overview of podophyllotoxin and different derivatives thereof, which are commercially derived from two species of plants, *Podophyllum peltatum* and *Podophyllum emodi.* As said, the cytotoxic effect of podophyllotoxin has been ascribed to its binding to microtubuli resulting in a mitotic block. The same effect on cells has been described for several of its derivatives such as deoxypodophyllotoxin.

The binding of certain amino-substituted 1-phenyl-1,2,3,4-tetrahydronaphtalenes to a receptor with σ-like neuromodulatory activity in the mammalian central nervous system has been studied by Wyrick, S.D., et al., Journal of Medical Chemistry 36 (1993), 2542-2551.

OBJECTS OF THE INVENTION

The object of the present invention is to find new compounds and new methods for treatment of IGF-1R dependent diseases, such as cancer, psoriasis and arteriosclerosis, by means of a specific inhibition of the insulin-like growth factor-1 receptor.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a computer model of a 12 amino acid peptide comprising the tyrosines 1131, 1135 an 1136 of the IGF-1 receptor.

Figure 2 shows the structural formulas of the cyclolignan podophyllotoxin and the new compound 12-THN, which is the 2,3-carbonyldioxy (carbonate) derivative of 2,3-dihydroxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene.

DESCRIPTION OF THE INVENTION

The three-dimensional structure of short peptides having the amino acid sequence of the IGF-1R tyrosine domain, including the tyrosine residues at position 1131, 1135 an 1136, was analysed using a computer programme in order to find compounds having the ability to mimic the tyrosine residues and interfere with their phosphorylation. It was then discovered when using a 12-amino acid peptide that two of the three key tyrosines, that is 1135 and 1136, which have to be autophosphorylated in IGF-1R for activation, could be situated as close as 0.95 nm (9.5 Å) from each other, and that the apparent angle between these groups was about 60°. The configuration of said sequence is shown in Figure 1. Such a short distance has not been observed for the corresponding tyrosines in the insulin receptor.

Molecular modelling showed that an inhibitory molecule could consist of two benzene rings separated by only one carbon atom. When a two-carbon bridge was tried, the distance between the substituents of the benzene rings was too long, about 1.3 nm (13 Å).

The substituents of the inhibitors corresponding to the hydroxy groups in the tyrosines were selected to be methoxy or methylenedioxy groups, since they are chemically relatively stable, i.e. they are not oxidized or phosphorylated. The distance between these substituents seems to be about 0.95 ± 0.10 nm (9.5 ± 1.0 Å).

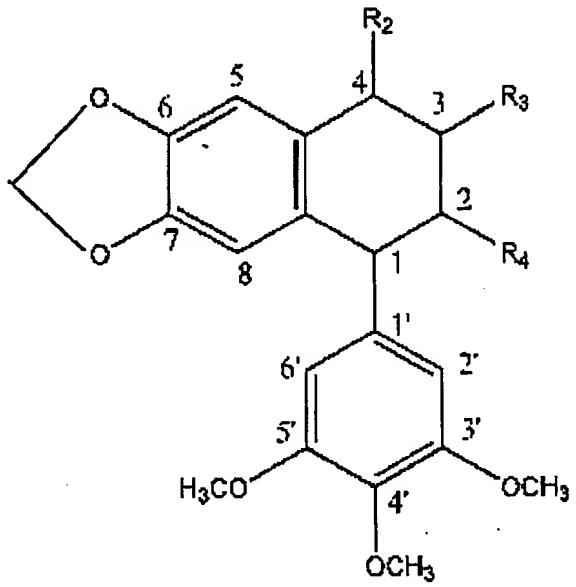
It was then surprisingly found that the two angled benzene rings of some cyclolignans, including podophyllotoxin, could mimic almost exactly the two tyrosines 1135 and 1136, indicating that said compounds may fit into the tyrosine kinase pocket and thereby interfere with the autophosphorylation of the tyrosine residues. Another group of compounds, which may mimic the tyrosines 1135 and 1136, was found to be substituted 1-phenyl-tetrahydronaphtalenes. Advantages with these compounds are that they lack a lactone ring and may therefore not be as cytotoxic as podophyllotoxin and in that they may be easier to synthesize. Figure 1 also shows the space structures of podophyllotoxin and the new compound 12-THN, which is the 2,3-carbonyldioxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene.

In order to penetrate the receptor and fit into the tyrosine pocket, one can expect that an inhibitory molecule has to be small. When for instance podophyllotoxin was conjugated with a glucoside derivative into podophyllotoxin-4,6-O-benzylidene-β-D-glucopyranoside, the effect on IGF-1R completely disappeared. Furthermore, following reduction of the lactone ring to a diol structure, the size of the molecule increased due to the reduced substituents sticking out from the molecule, resulting in a dramatically reduced activity of the compound.

The inhibitor molecule also has to be relatively nonpolar, so that it can freely penetrate cell membranes and the IGF-1 receptor, but sufficiently polar to be reasonably soluble in water. The polarity of the molecule is determined by the number and nature of the oxygen functions. The polarity seems to be optimal when the

water solubility is between 0.01 mM and 0.1-0.2 mM. No charged or highly polar groups should be present in the molecule.

The invention refers to a compound of the formula I



I

wherein R_2 is H, O or OH, and R_3 and R_4 together are methylenedioxy, carbonyldioxy (carbonate) or dimethyl-methylenedioxy (acetonide); or R_2 and R_3 together are methylenedioxy, carbonyldioxy or dimethyl-methylenedioxy and R_4 is H, O or OH; or each is lower alkoxy; or R_2 is OH and R_3 and R_4 are H; or R_2 is O and R_3 and R_4 are H; or R_3 is O and R_2 and R_4 are H; or R_2 and R_3 are OH and R_4 is H; with the proviso that when R_3 and R_4 together are methylenedioxy, R_2 is not H. Said compound can be used as a specific inhibitor of tyrosine phosphorylation of the insulin-like growth factor-1 receptor.

The invention especially refers to the following substances:

4-hydroxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene;

3,4-dihydroxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene;

3-oxo-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene;
4-oxo-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene.

2,3-dimethoxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene;
4-hydroxy-2,3-dimethoxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene;
2,3-dimethoxy-4-oxo-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene.

The 2,3-methylenedioxy derivative of:
2,3-dihydroxy-4-oxo-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene;
2,3,4-trihydroxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene.

The 3,4-methylenedioxy derivative of:
3,4-dihydroxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene;
3,4-dihydroxy-2-oxo-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene;
2,3,4-trihydroxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene.

The 2,3-carbonyldioxy (carbonate) derivative of:
2,3-dihydroxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene;
2,3-dihydroxy-4-oxo-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene;
2,3,4-trihydroxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene.

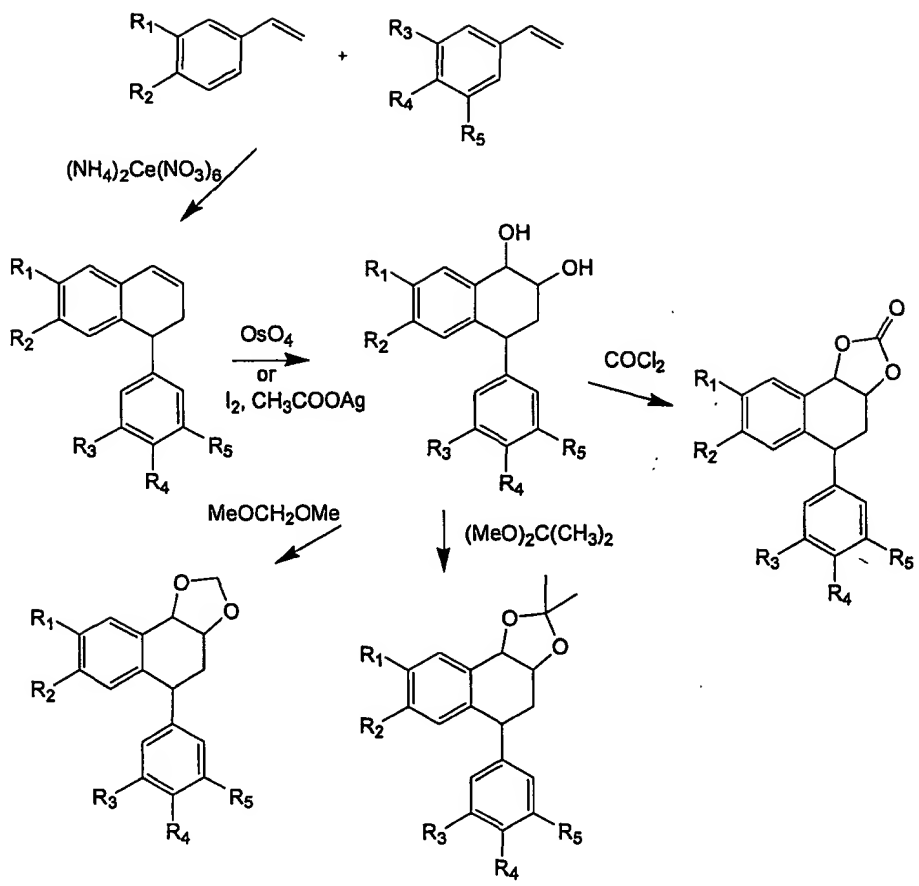
The 3,4-carbonyldioxy (carbonate) derivative of:
3,4-dihydroxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene;
3,4-dihydroxy-2-oxo-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene;
2,3,4-trihydroxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene.

The 2,3-dimethyl-methylenedioxy (acetonide) derivative of:
2,3-dihydroxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene;
2,3-dihydroxy-4-oxo-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene;
2,3,4-trihydroxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene;

The 3,4-dimethyl-methylenedioxy (acetonide) derivative of:
3,4-dihydroxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene;
3,4-dihydroxy-2-oxo-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene;
2,3,4-trihydroxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphtalene.

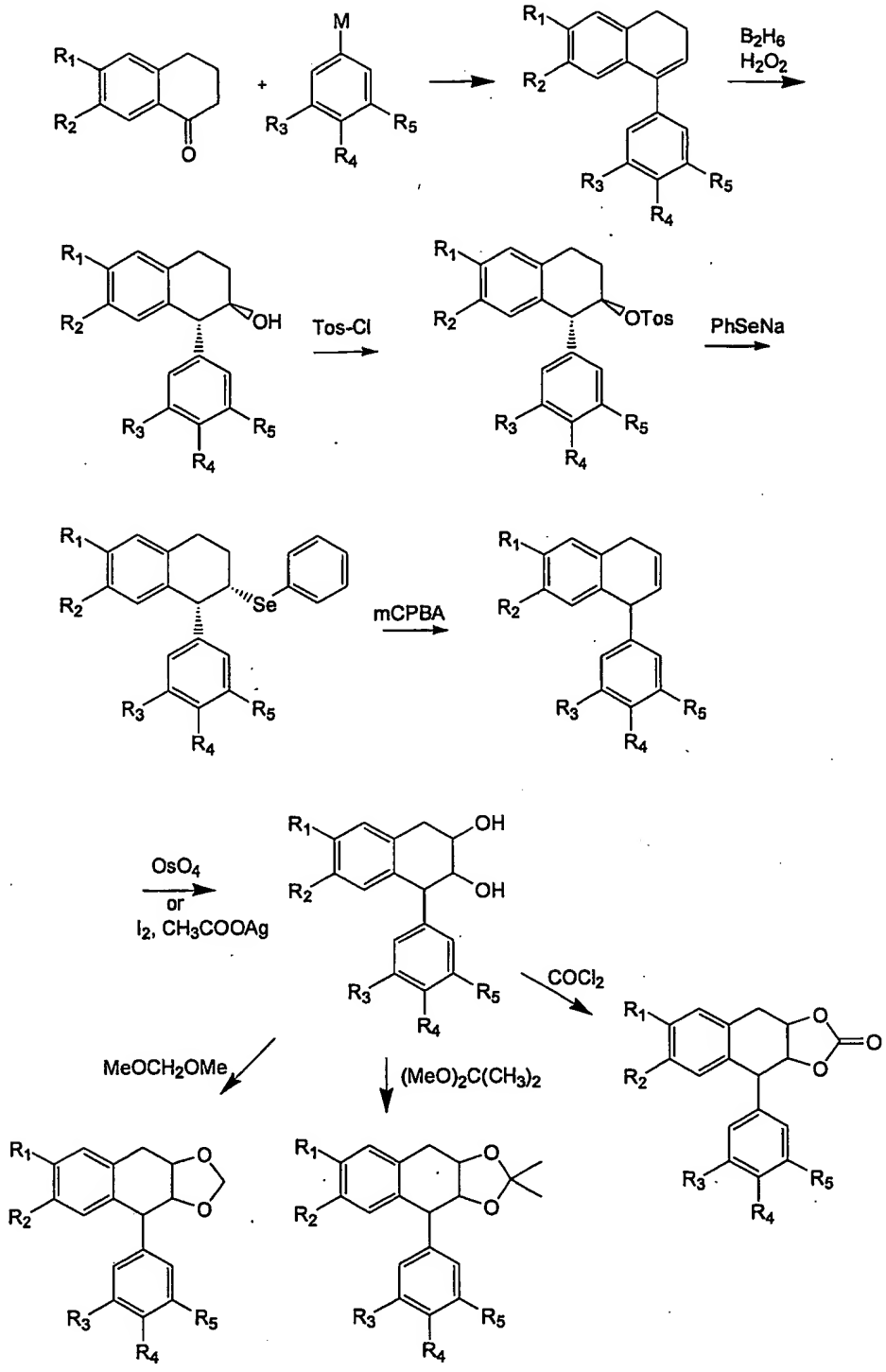
The compounds of the formula I especially can be used as specific inhibitors of the tyrosine autophosphorylation of the insulin-like growth factor-1 receptor, since the use of more cytotoxic and tissue irritating compounds, such as the cyclolignan podophyllotoxin should be avoided.

Compounds of formula I may be prepared according to representative syntheses depicted in Schemes 1 and 2:



Scheme 1

1-Phenyl-1,2-dihydronaphtalenes are known, see for example: Nair, V., et al.: Tetrahedron Letters (1977), 38(12), 2191-2194. Hydroxylation with OsO_4 gives the cis-hydroxyl product, whereas I_2/CH_3COOAg give trans. Stereoisomers will also be obtained relative to the phenyl group, depending on from which side the hydroxylation reagent attacks. This is also true for scheme 2 below. All such isomers are meant to be included in the reaction schemes.



Scheme 2

The first steps in this synthesis have been described in Heterocycles (1984), 22(2), 311-31 by G. Laus et al. The reactions outlined above are well known in the art, see e.g. Advanced Organic Chemistry, Jerry March (ed.) 4th edition, Wiley-

Interscience Publication, New York 1992.

We have now demonstrated that podophyllotoxin and some of its analogues are very potent inhibitors of tyrosine phosphorylation of the insulin-like growth factor-1 receptor, which plays a pivotal role as a survival factor in cancer cells. Their actions are also very specific for the IGF-1R in that sense that they do not cross-react with the insulin receptor, which is highly homologous to IGF-1R. Moreover, they do not inhibit other major growth factor receptor kinases either. Podophyllotoxin has been implicated in cancer therapy, but when it was administered to patients it produced severe and unacceptable side effects. The anti-cancer effect, as well as the side effects, was attributed to inhibition of microtubule assembly and mitotic block. Substituted 1-phenyl-tetrahydronaphtalenes are structurally very similar to the cyclolignans such as podophyllotoxin, but have a 16-carbon skeleton instead of a 18-carbon skeleton. More important is that they lack the lactone ring which is essential for binding to microtubuli and therefore they can be much less cytotoxic than the cyclolignans.

Relatively nontoxic compounds of the formula I can therefore be used for treatment of IGF-1R dependent diseases, such as cancer, arteriosclerosis, including prevention of restenosis of the coronary arteries after vascular surgery, psoriasis and acromegaly. The invention thus refers to the new compounds of the formula I for use as a medicament, and especially for the preparation of a medicament for treatment of cancer, arteriosclerosis, psoriasis and acromegaly. The term cancer is used here in a broad sense including carcinomas, i.e. tumours of epithelial origin such as prostatic, breast, gastrointestinal and lung tumours; sarcomas, i.e. mesenchymal tumours such as malignant fibrous histiocytoma and liposarcoma; neuroectodermal tumours such as malignant melanoma, Ewing sarcoma and neuroblastoma; gliomas such as glioblastoma multiforme, astrocytoma and medulloblastoma; myeloproliferative

diseases such as myeloma and myeloid leukemia; and lympho-proliferative diseases such as Hodgkin and non-Hodgkin lymphoma and lymphatic leukemia.

In case of tumour cells not completely dependent on IGF-1R for their survival, the compounds of the invention can be useful to potentiate the effects of other anti-cancer drugs and treatments. The invention therefore also refers to the use of a compound of the formula I in combination with another cytostaticum. As examples of cytostatica, which can be used together with the compounds of the invention, can be mentioned vincristin, taxol and etoposide.

For parenteral administration, the compounds may be administered as injectable dosages or by continuous, intravenous infusion of a solution, suspension or emulsion of the compound in a physiologically acceptable diluent as the pharmaceutical carrier, which can be a sterile liquid, such as water, alcohols, oils, emulsions, and other acceptable organic solvents, with or without the addition of a surfactant and other pharmaceutically acceptable adjuvants.

The compounds can also be administered in the form of a depot injection or implant preparation, which may be formulated in such a manner as to permit a sustained release of the active ingredient.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, troches, powders, solutions, suspensions or emulsions.

For topical application the compounds can be administered in the form of an unguent, cream, ointment, lotion or a patch.

Biological experiments suggest that submicromolar concentrations of the new compounds can be sufficient to cause tumour cell death. However, it is believed that it is important to keep a constant, not too low, plasma concentration of the inhibitors over lengthy periods, to allow them to continuously saturate and block all IGF-1Rs, and in this way eventually kill as many malignant cells as possible. Therefore, continuous infusion of the compound

of the invention, in connection with monitoring the plasma concentration, may be the strategy of treatment instead of giving one single or repetitive injections with relatively long time intervals, for instance once daily or weekly, which may lead to repeated reactivations of IGF-1R between the treatments.

The invention consequently also refers to a method of treatment of a cancer in a mammal, comprising the steps of administrating a pharmaceutical composition, containing a compound having the formula I in combination with a physiologically acceptable carrier, by constant infusion to a patient suffering from a tumour, monitoring the plasma level of the compound, and adjusting the rate of infusion to keep the plasma level between 0.05 and 5.0 μM depending on the potency and the general toxicity of the compound, for a period of time being required for the tumour to be retarded or to disappear.

Example. Preparation of 3,4-dimethyl-methylenedioxy-1-(3',4'-dimethoxy-phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene

1.63 g (5.0 mmol) of 1-(3,4-dimethoxy-phenyl)-6,7-dimethoxy-1,2-dihydronaphthalene (prepared as described in Tetrahedron Letters (1977), 38(12), 2191-94, by V. Nair *et al.*) was dissolved in dry pyridine (50 ml) and to this was added a solution of OsO_4 (2 g, 7.9 mmol) in dry THF (50 ml). The mixture was left in the dark and at room temperature for 48 h with occasional stirring. Aqueous $NaHSO_3$ (8 g in 60 ml of water) was added and the mixture was stirred for 3 h, diluted with water and extracted with ethyl acetate. The organic layer was washed with 10 % HCl and brine, dried with Na_2SO_4, filtered and the solvents were evaporated to give a residue which was purified by chromatography, yielding 0.4 g of 3,4-dihydroxy-1-(3',4'-dimethoxy-phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene.

0.4 g (1.1 mmol) of 3,4-dihydroxy-1-(3',4'-dimethoxy-phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene was dissolved in dry CH_2Cl_2 (15 ml) and DMF (4 ml) and to the reaction mixture was added 2,2-dimethoxypropane (4 ml) and p-TsOH (0.1 g). The mixture was stirred for 6 h at room temperature. Aqueous $NaHCO_3$ was added and the mixture was extracted with ether. The organic layer was washed with brine, dried with Na_2SO_4 and the solvents were evaporated. The residue was purified by chromatography yielding 0.3 g of 3,4-dimethyl-methylenedioxy-1-(3',4'-dimethoxy-phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene.

Using the appropriate starting materials the following new compounds can be prepared in a similar way as the compound described above:

3,4-dihydroxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy - 1,2,3,4-tetrahydronaphthalene;

3,4-methylenedioxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene;

3,4-carbonyldioxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene;

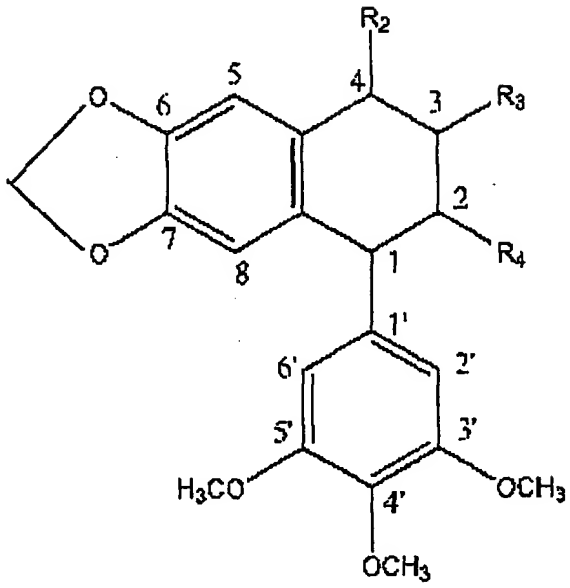
3,4-dimethyl-methylenedioxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene;

2,3-carbonyldioxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene;

2,3-dimethyl-methylenedioxy-1-(3',4',5'-trimethoxy-phenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene.

CLAIMS

1. A compound having the formula I



I

wherein R_2 is H, O or OH, and R_3 and R_4 together are methylenedioxy, carbonyldioxy or dimethyl-methylenedioxy; or R_2 and R_3 together are methylenedioxy, carbonyldioxy or dimethyl-methylenedioxy and R_4 is H, O or OH; or each is lower alkoxy; or R_2 is OH and R_3 and R_4 are H; or R_2 is O and R_3 and R_4 are H; or R_3 is O and R_2 and R_4 are H; or R_2 and R_3 are OH and R_4 is H; with the proviso that when R_3 and R_4 together are methylenedioxy, R_2 is not H.

2. A compound of the formula I for use as a medicament.

3. A pharmaceutical composition comprising a compound of the formula I in combination with a physiologically acceptable carrier.

4. Use of a compound of the formula I for the preparation of a medicament for treatment of IGF-1R dependent diseases, such as cancer, arteriosclerosis, psoriasis and acromegaly.

5. Use of a compound according to claim 1 in combination with a cytostaticum for treatment of cancer.

6. Method of treatment of a cancer in a mammal, comprising the steps of administrating a pharmaceutical composition, containing a compound having the formula I as defined in claim 1 in combination with a physiologically acceptable carrier, by constant infusion to a patient suffering from a tumour, monitoring the plasma level of the compound, and adjusting the rate of infusion to keep the plasma level at a relatively constant concentration of 0.05-5.0 μM dependent on the potency and toxicity of the compound, for a period of time being required for the tumour to be retarded or to disappear.

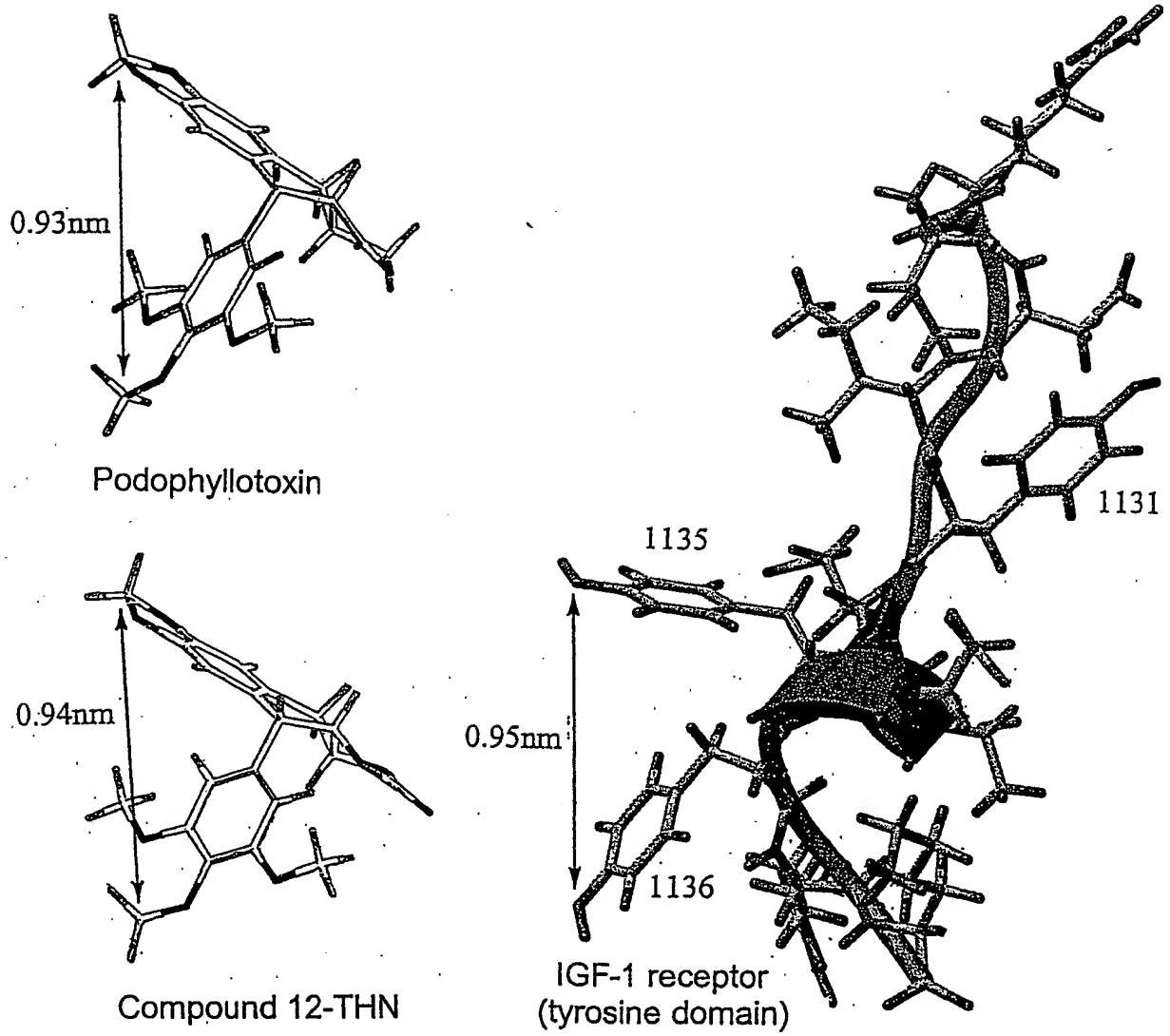
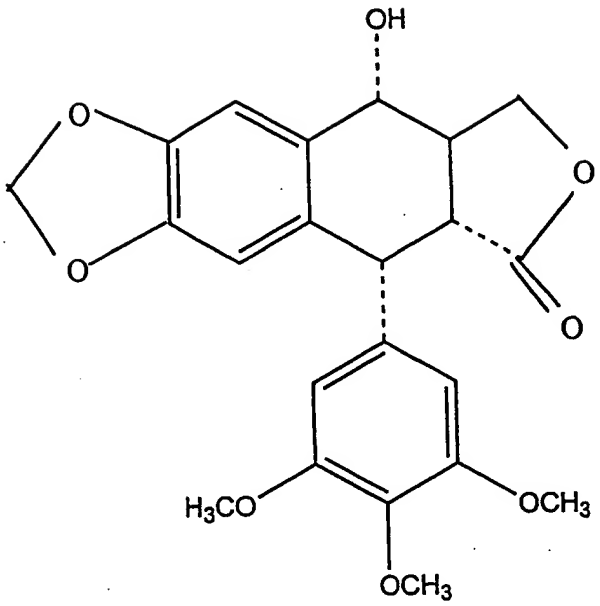
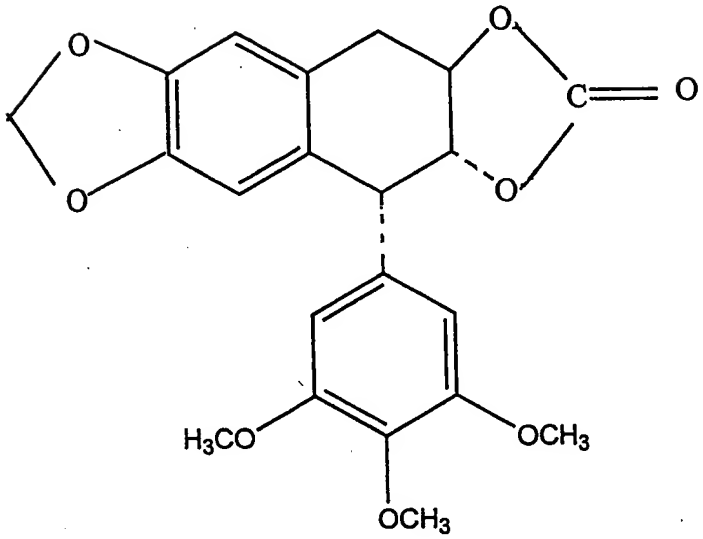

0.93nm
Podophyllotoxin
0.94nm
Compound 12-THN
1135
1131
0.95nm
1136
IGF-1 receptor
(tyrosine domain)

FIG. 1



Podophyllotoxin



Compound 12-THN

FIG. 2

INTERNATIONAL SEARCH REPORT

Internauonal application No.
PCT/SE 2003/002010

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 317/48, C07D 493/06, A61K 31/36, A61P 17/06
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM. ABS DATA, WPI DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02102805 A1 (KAROLINSKA INNOVATIONS AB), 27 December 2002 (27.12.2002) --	1-6
X	Tetrahedron, Volume 53, no. 46, 1997, Marina Gordaliza et al: "Preparation and Cytotoxicity of Podophyllotoxin Derivatives Lacking the Lactone Ring", page 15743 - page 15760 --	1-6
A	US 4788216 A (KURT LEANDER ET AL), .29 November 1988 (29.11.1988) -- --------	1-6

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 March 2004	16 -03- 2004
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carolina Gómez Lagerlöf/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/002010

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 6
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/002010

Box No. IV Text of the abstract (*Continuation of item 5 of the first sheet*)

Claim 6 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practised on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds or compositions.

WO	02102805	A1	27/12/2002	AU	9446001	A	15/04/2002
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				EP	1325035	A	09/07/2003
				SE	0102168	D	00/00/0000
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				AT	68186	T	15/10/1991
				AU	585936	B	29/06/1989
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				ZA	8509881	A	24/09/1986